A Versatile and Convenient Method for the Preparation of α-(*Z*)-1-Alkenyl Ketones from β-Keto Benzyl Esters

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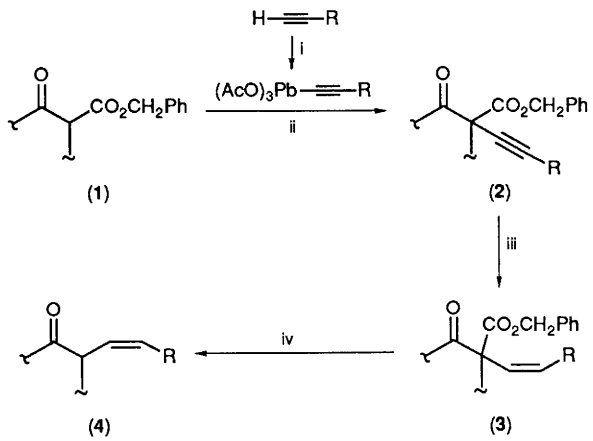
A versatile and selective method for the preparation of α-(*Z*)-1-alkenyl ketones from β-keto benzyl esters has been developed by exploiting the three-step sequence of an improved Pinhey's alkynylation, semihydrogenation, and reductive debenzyloxycarbonylation.

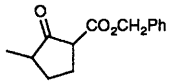
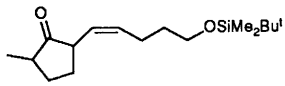
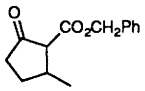
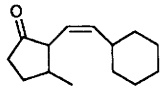
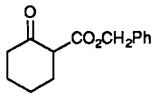
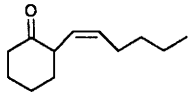
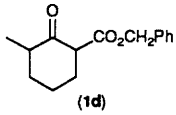
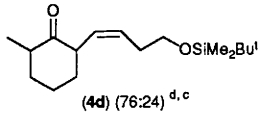
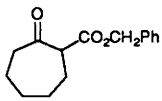
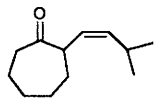
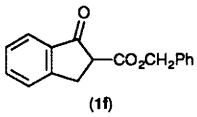
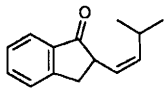
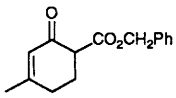
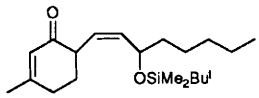
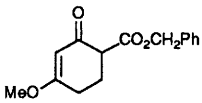
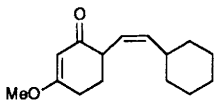
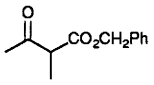
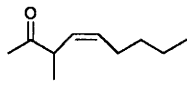
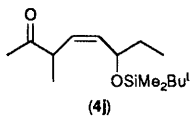
The synthetic utility of α-alkenyl ketones as valuable intermediates for a wide range of transformations, particularly ring expansion reactions *via* Cope,[1] anionic oxy-Cope,[2] or Cope–Claisen[3] rearrangement, has sparked development of new and expedient methods for their preparation. Despite the many advances,[4] however, there still remains a need for developments in terms of generality, practicality, and selectivity. We recently devised a facile and controlled method for the synthesis of α-(*E*)-1-alkenyl ketones from β-keto benzyl esters *via* improved Pinhey's alkenylation with the alkenyl-lead(IV) reagent prepared *in situ* from (*E*)-1-alkenylzinc chloride and lead tetra-acetate, and reductive debenzyloxycarbonylation.[5] Here we report a versatile and convenient method for the preparation of α-(*Z*)-1-alkenyl ketones from β-keto benzyl esters.

Our initial attempt to prepare α-(*Z*)-1-alkenyl ketones *via* a similar strategy to that in the synthesis of α-(*E*)-1-alkenyl ketones met with failure, simply because the introduction of (*Z*)-1-alkenyl groups onto β-keto benzyl esters did not proceed. We then focused our efforts on the development of a three-step procedure of α-alkynylation of β-keto benzyl esters, semihydrogenation, and debenzyloxycarbonylation (Scheme 1). For the introduction of alkynyl groups onto β-keto esters,[6,7] although Pinhey's alkynylation[6] using the 'alkynyl-lead(IV) triacetates' prepared *in situ* from alkynyltrialkylstannanes and lead tetra-acetate was the method of choice, the method required the separate synthesis of moisture-sensitive alkynylstannanes, and the formation of trialkyltin acetates as by-products made the purification of the products tedious. Since the efficacy of alkynylation reactions is crucial to the success of our scenario, we attempted to develop a more convenient and straightforward method for the generation of 'alkynyl-lead(IV) triacetate' without attendant formation of side-products. Toward this end, the reaction of a mixture of lead tetra-acetate and each of hexynylmetals containing Li, MgBr, Cu(CN)Li, ZnCl, $AlEt_2$ *etc.* with benzyl 2-oxocyclohexanecarboxylate (**1c**) was explored.



Scheme 1. *Reagents and conditions*: i, Bu^nLi (1.55 equiv.), tetrahydrofuran (THF), −30 °C, 0.5 h; $Pb(OAc)_4$ (1.5 equiv.), CH_2Cl_2, 23 °C, 15 min; ii, CH_2Cl_2–THF (5 : 1), 23 °C, 0.5 h; iii, H_2, Lindlar catalyst, benzene, 23 °C, 1 h; iv, W-2 Raney nickel (5—10 ml of sediment in EtOH per mmol), Et_3N (0.2 equiv.), 23 °C, 0.5 h.

Table 1. Synthesis of α-(*Z*)-1-alkenyl ketones (**4**) from β-keto benzyl esters (**1**).[a]

Entry	β-Keto ester (1)	R	Adduct (2) (% yield)	Product (4)	% Yield [b] (*Z*:*E*) [c]
1	 (1a)	$(CH_2)_2CH_2OSiMe_2Bu^t$	(2a) (84)	 (4a) (60:40) [d,c]	75 (95:5)
2	 (1b)	$c\text{-}C_6H_{11}$	(2b) (84)	 (4b) (5:95) [d,c]	83 (98:2)
3	 (1c)	Bu^n	(2c) (88)	 (4c)	76 (95:5)
4	 (1d)	$CH_2CH_2OSiMe_2Bu^t$	(2d) (92)	 (4d) (76:24) [d,c]	70 (94:6)
5	 (1e)	Pr^i	(2e) (90)	 (4e)	78 (97:3)
6	 (1f)	Pr^i	(2f) (82)	 (4f)	79 (97:3)
7	 (1g)	$CH(CH_2)_3CH_2Me$ $OSiMe_2Bu^t$	(2g) (78)	 (4g)	85 (98:2)
8	 (1h)	$c\text{-}C_6H_{11}$	(2h) (82)	 (4h)	77 (96:4)
9	 (1i)	Bu^n	(2i) (82)	 (4i)	74 (95:5)
10	(1i)	$CH(OSiMe_2Bu^t)Et$	(2j) (79)	 (4j)	82 (99:1)

[a] The alkynyl-lead(IV) reagent (1.5 equiv.) was used except in entries 1 and 2 (2.0 equiv.), and in entry 6 (2.5 equiv.). [b] Based on the adduct (**2**). [c] The ratio was determined by ^1H NMR analysis. [d] *cis* : *trans* ratio of ring substituent isomers.

Interestingly, hexynyl-lithium was found to be the reagent of choice among the metals screened. Thus, coupling of (**1c**) (1.0 equiv.) with the hexynyl-lead(IV) reagent generated *in situ* by addition of a precooled solution of hexynyl-lithium, prepared from hex-1-yne (1.55 equiv.) and n-butyl-lithium (1.55 equiv.), in tetrahydrofuran (THF) to a solution of lead tetra-acetate (1.5 equiv.) in dichloromethane at −20 °C followed by stirring at 23 °C for 15 min proceeded smoothly at

23 °C within 0.5 h to give the desired adduct (**2c**)† in 88% yield. Clearly, the direct preparation of the alkynyl-lead(IV) reagent offers distinct advantages over the original procedure. Some representative results based on the improved method are summarized in Table 1, in which the widespread applicability of this method is amply demonstrated. Particularly noteworthy, while the mechanistic profile is not clear at present,‡ is that the alkynylation reactions of an acyclic β-keto benzyl ester (**1i**) worked well (entries 9 and 10), whereas the original Pinhey's method was found to give much inferior results.

Partial catalytic reduction of the adducts (**2**) thus obtained in benzene over Lindlar catalyst followed by reductive removal of the benzyloxycarbonyl group with W-2 Raney nickel in ethanol in presence of triethylamine furnished the corresponding α-(*Z*)-1-alkenyl ketones (**4**) in good yields and with 94—99% stereoisomeric purities, which were in accord with the degrees of the stereoselectivity of the former reaction. As can be seen from Table 1, the present method allows for considerable variation in both β-keto benzyl esters and (*Z*)-1-alkenyl groups. Furthermore, this method coupled with Mander's method[8] for regiocontrolled benzyloxycarbonylation[9] constitutes a convenient procedure for the controlled α-(*Z*)-1-alkenylation of unsymmetrical cyclic ketones.

† All new compounds were fully characterised by ^{1}H NMR (400 MHz), IR, and high resolution mass spectral analysis. Yields refer to spectroscopically and chromatographically homogeneous materials.

‡ Lithium acetate formed during the preparation of the alkynyl-lead(IV) reagents might be responsible for smooth alkynylation as indicated by the following results; alkynylation of (**1i**) (1.0 equiv.) with the hexynyl-lead(IV) reagent generated *in situ* from tributyl-(hexynyl)stannane (1.55 equiv.) and lead tetra-acetate (1.5 equiv.) in chloroform in the absence or presence of lithium acetate (1.5 equiv.) produced the adduct (**2i**) in 14 and 81% yields, respectively.

In summary, the three-step protocol based on readily available substrates and reagents has the advantages of operational simplicity and practical value as well as a selective entry to a variety of α-(*Z*)-1-alkenyl ketones.

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